Host CCR5 and HIV-1 env/pol Polymorphisms: Role in transmission and virulence in the Kenyan population

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Abstract

INTRODUCTION

HIV-1 env protein and host cluster of differentiation antigen 4 (CD4) and wild-CC chemokine receptor 5 (CCR5) proteins are responsible for the attachment and entry of HIV-1 into T lymphocytes, hence influencing its infectivity. However, information on the flow, distribution, ARVs resistance patterns and co-infections of the HIV-1 sub-types is limited. An up-to-date comprehensive review on the role of CCR5/CD4 and env/pol protein polymorphisms in the susceptibility to HIV-1 infection, virulence, transmission, disease progression and discordance in the Kenyan population is lacking. This study aimed to review the role of CCR5/CD4 and HIV-1 env/pol protein polymorphisms in the transmission and virulence of HIV-1 in the Kenyan population.

METHODOLOGY

Data was sourced by literature search on Google Scholar, PubMed, and ScienceDirect. Grey literature articles were manually reviewed. Study selection was based on relevance to the role of CCR5/CD4 and env/pol protein polymorphisms in the transmission and virulence of HIV-1 were included in the review. Data were extracted from individual studies or articles. Data were synthesized regarding the information on the role of CCR5/CD4 and env/pol protein polymorphisms in the transmission and virulence of HIV-1 is synchronized under the headings; introduction, molecular characterization of HIV-1, HIV-1 treatment and antiretrovirals (ARVs) resistance, influence of host genes on HIV-1 disease progression, CD4 as HIV-1 receptors, and characterization of genetic/antigenic variants circulating in a given population.

RESULTS

A total of 74 articles were screened and 66 eligible articles were reviewed, four (4) of them touching on the origin and evolutionary mechanisms of the human immunodeficiency virus (HIV), while 21 articles addressed molecular characterization of the HIV-1. A total of 11 articles addressed HIV-1 treatment and ARVs resistance whereas 13 articles addressed the influence of host genes on HIV/AIDS disease progression. Eleven (11) and 8 articles addressed the CD4 as HIV-1 receptors and characterization of HIV-1 genetic/antigenic variants circulating in a given population, respectively.

CONCLUSION

There are many HIV-1 subtypes in circulation in Kenya with uneven distribution and it is difficult to accurately predict future metamorphosis and determine and monitor the flow and ARVs resistance patterns of the sub-types.
A mutant allele of the β-chemokine receptor gene CCR5 prevents cell invasion and homozygotes for this mutation are resistant to infection with heterozygosity at this gene correlating with slowed HIV/AIDS disease progression. The C868T single nucleotide polymorphism (SNP) in CD4 increases the risk of HIV-1 acquisition.

RECOMMENDATIONS

There is a need for accurate prediction of the future metamorphosis and regular evaluation and monitoring of the flow, distribution, ARVs resistance patterns and co-infections of the HIV-1 sub-types and their variation over time. Detailed assessment of the role of CCR5/CD4 and env/pol protein polymorphisms in the susceptibility to HIV-1 infection, virulence, disease progression and discordance in some couples in the Kenyan population is important.

Key words: HIV-1 Subtypes, ARVs Resistance, CD4 as HIV-1 Receptors, CCR5/CD4 and HIV-1 env/pol Protein Polymorphisms, Kenya

[Introduction]

The origin and evolutionary mechanisms of the human immunodeficiency virus (HIV) remain mind-boggling. The theories of the origin and evolutionary relationship between HIV-1, HIV2 and the simian immunodeficiency virus (SIV) are based on seroepidemiological and viral genome molecular data. The existing data support the theory of transmission of SIV to humans becoming HIV-2, followed by its rapid evolution to HIV-1 with an explosive escape from an isolated human population [1, 2]. HIV has just nine (9) genes, compared to about 25,000 protein-coding genes in a human. Three of the HIV-1 genes, gag, pol and env, code for structural proteins for new virus particles. The other six genes, tat, rev, nef, vif, vpr and vpu, code for proteins that control the ability of HIV to infect a cell, produce new copies of the virus, or cause disease. At either end of each strand of RNA is the long terminal repeat sequence, which helps to control HIV-1 replication [3]. However, reverse transcription (RNA → DNA) in HIV lacks the proofreading capabilities of DNA replication or of normal DNA → RNA transcription. The resultant numerous errors in reverse transcription lead to mutations responsible for the frequent HIV-1 genetic variability [4]. Why mutations which are usually detrimental in most organisms appear to be beneficial for HIV-1 is confounding.

[Methodology]

References obtained through examining relevant bibliographies were included in this review. The articles reviewed included those touching on the molecular characterization of the HIV-1, HIV-1 treatment and antiretrovirals (ARVs) drug resistance, the influence of host genes on HIV/AIDS disease progression, CD4 as HIV-1 receptors, and characterization of HIV-1 genetic/antigenic variants circulating in a given population. We assumed that different HIV-1 subtypes exhibiting varied ARVs resistance patterns are in circulation in the Kenyan population, and periodic genetic variations lead to serial mutations that are associated with the HIV-1 subtype variants and ARV resistance. It was also our assumption that polymorphisms in the host CD4 / CCR5 and HIV-1 env/pol proteins are responsible for the variations in the transmission, virulence of HIV-1 subtypes and HIV/AIDS discordance seen in some couples in the Kenyan population.

Molecular characterization of HIV-1

Molecular analysis of HIV-1 and HIV-2 subtypes has revealed the global epidemic to be composed of multiple genetically distinct virus
sub-epidemics [5, 6, 7]. The HIV-2 prevalence is reported to be highest in the West African countries [5, 6]. Genotyping of HIV-1 around the world shows that the prevalence of different clades in different countries is strikingly non-uniform. Clade B predominates in Western Europe and North America; Clades A and D predominate in most of sub-Saharan Africa; Clade C predominates in Southern Africa, the Horn of Africa and West Africa, and Clade E/A predominates in Southeast Asia. The most complex epidemic is in Central Africa, where rare subtypes and a wide variety of recombinant forms circulate without any discernable predominant strain. However, HIV-1 genotypes A through H have all been detected in the Equatorial African region [8]. The “cosmopolitan clade B” predominates in other regions of the world including South America, Australia, Japan and China. HIV-O (HIV-1 Outlier) strains have been detected only in Gabon, Cameroun, Equatorial Guinea, and in people who have visited these countries. Studies have also demonstrated co-infection with group M and a recombinant M/O virus [9].

Recombination between strains with such distant linkage (65% overall homology) may contribute substantially to the emergence of new HIV-1 variants, with serious implications for serological and molecular diagnosis of HIV-1 infections, and treatment [10]. Genetic studies have also shown that HIV-1 and HIV-2 co-infection may not be a static condition. It is suspected that levels of HIV-2 may decrease with the progression of the disease or sequester in tissue reservoirs, or HIV-1 may effectively outgrow HIV-2 in co-infected individuals [11].

In East Africa, studies show variations of HIV-1 subtypes by country, with subtypes A, C, G and AD recombinants being predominant in Kenya, subtypes A, D and AD recombinants in Uganda and subtype C and AC recombinants in Tanzania [12]. In the coastal region of Kenya, studies have reported HIV-1 subtypes A1, C, D, and G, [13, 14] with a large proportion being recombinants [14]. These studies show the HIV-1 subtype A1 to be the most dominant subtype in circulation in this region. In the northern border with Ethiopia, subtypes A, C and D are the dominant. The Ethiopian side is dominated mainly by HIV-1 subtype C, which incidentally is the dominant subtype in the border town of Moyale, an indication that cross-border movements play an important role in the circulation of the HIV-1 subtypes [15].

Genetic studies in the Rift Valley region report HIV-1 subtypes A1, C, D, G, various recombinants [16, 17] and A2, A1D, A1C, A2C [16]. Subtypes A1, D, C, G, CRF 21A2D, CRF 16A2D, and subtype B have been reported from the Nyanza region. Unique recombinants A1D, A1C, D01AE, A1B, and DB have also been reported [17]. Kageha et al. [18] report the HIV-1 subtypes A, C and D to be in circulation in Central Kenya.

The Nairobi region is dominated by genetically diverse clade A. Additionally, the prevalence of highly divergent, complex subtypes, inter-subtypes, and recombinant forms indicates viral mixing in the Kenyan population, possibly as a result of dual infections [19]. Similarly, a study by Lihana et al. [20] in the same region reports HIV-1 subtypes A1/A1, A/C, A1/D, C/D, D/D, A1/A2, G/G, A2/D, C/C, and CRF02_ AG to be in circulation. The western Kenya region has the HIV-1 subtypes A1, B, C, D, [21, 22, 23], subtypes A2 [20, 21], and subtypes G, [22, 23, 24] and unclassified unique recombinants were recently reported [23]. Also reported are recombinants CRF A1_D [21], A1/C, A1/D [22, 23], and inter-subtype recombinants A1-B, A1-A2, A1-C, BC and BD [23].

However, with the increased mobility of the global population, this geographic distribution of HIV-1 clades is bound to change...
over time. Also, drug users act as reservoirs and transmission channels for HIV-1 infections and other viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV) and the general population worldwide. However, Periodic epidemiological studies to monitor the prevalence and genetic diversity of these infections to inform interventions are limited [25].

**HIV-1 treatment and antiretroviral (ARVs) resistance**

Antiretroviral therapy (ART) has transformed HIV infection into a treatable, chronic condition [26]. However, the occurrence of mutations that cause resistance to ARVs can limit the efficacy of ART regimens. Most drug-resistant mutants of HIV-1 emerging under the selective pressure of prolonged chemotherapy are due to mutations in the HIV-1 pol gene that encodes for the reverse transcriptase (RT) enzyme [27]. Sometimes recombination between strains from various regions may contribute substantially to the emergence of new HIV-1 variants including those resistant to ARVs [10].

Since ART treatment will be continued for many decades, the development of resistance to ARVs is eminent, and will adversely affect the efficacy of the ARVs. The great heterogeneity and emergence of many HIV-1 recombinants all over the world also mean different responses by patients to ART and different immune responses to the recombinants [28, 29]. It may be important to determine whether mutations in HIV are random or follows a certain pattern.

Studies have been done to measure the prevalence of ARVs drug-resistant (ARVDR) HIV-1 to some of the drugs, but true estimates of ARVDR prevalence among patients receiving ARV therapy (ART) are limited [30]. However, ARV resistance highly correlates with specific ARV exposure [31, 32], and transmission of ARV-resistant HIV-1 strains may increase as therapy becomes more widespread [33]. Boyle [34] has reported that HIV-1 in patients who remain on stable ARV therapies in the face of viral replication evolves resistance-associated mutations over time. The rate of evolution appears to be influenced by HIV RNA level and CD4 cell count. Smith et al. [30] suggest that a high proportion of persons receiving ART in some settings could potentially transmit drug-resistant HIV. The HIV-1 variants with some specific drug-resistant genotypes are more efficiently transmitted than viruses with other drug resistance mutations. For instance, those with 41L, 215Y/F and 181C in the Reverse transcriptase (RT) gene, and 46L in the protease gene appear to be transmitted to a greater degree than were viruses with other drug resistance mutations, namely 184V and 103N in the RT gene and 82A/S/T and 90M in the protease gene [35].

**Influence of host genes on HIV/AIDS disease progression**

Host genes may influence HIV-1 infection and disease progression. Several chemokine receptors have been shown to serve as HIV-1 cell entry cofactors. However, the CCR5 chemokine receptor appears to be the main coreceptor for macrophage-tropic HIV-1, even though some HIV-1 isolates are dual tropic in being able to use both CCR5 and CXCR4 receptors. A mutant allele of the β-chemokines receptor gene CCR5 bearing a 32-basepair (bp) deletion (denoted delta ccr5) which prevents cell invasion by the primary transmitting strain of HIV-1 has been described. This mutated allele produces a truncated form of the protein that is not expressed on the cell surface. Hence, homozygotes for this mutation are resistant to infection, even after repeated high-risk exposures [36, 37, 38, 39, 40]. Heterozygosity at this gene correlates with slowed HIV/AIDS disease progression [41] implying that patient genotyping
A limited proportion of HIV-1 strains can also use additional chemokine receptors CCR3, CCR2b, and possibly CCR1 [43, 44]. A longitudinal study of children with progressive HIV-1 infection demonstrated that viral isolates obtained during asymptomatic stages generally used only CCR5 as a co-receptor whereas the majority of the strains derived after the progression of the disease had acquired the ability to use CXCR4 and, in some cases, CCR3, while gradually losing CCR5 usage [45, 46].

In Kenya, a study on commercial sex workers has shown heterozygous women for CD4 C868T to be more than twice more likely to acquire HIV than those with the wild-type CD4 allele. Given the high prevalence of both HIV-1 infection and CD4 C868T in African populations, the effect of SNP on the epidemic in Africa could be dramatic [47]. However, the uneven distribution and prevalence of HIV/AIDS in various Kenyan populations are speculated to be due to differences in socio-cultural practices, economic activities and status in the various communities [48].

The CD4 as HIV-1 receptors

The CD4 is a primary receptor used by HIV to gain entry into host T cells. HIV-1 attaches to CD4 with the gp120 protein in its viral envelope [49]. The binding to CD4 creates a shift in the conformation of the gp120 allowing HIV-1 to bind to two other surface receptors on the host cell, the chemokine receptors CCR5 or CXCR4, depending on whether HIV is infecting a macrophage or T-helper cell. Following a structural change in another viral protein (gp41), HIV-1 inserts a fusion peptide into the host cell that allows the outer membrane of the virus to fuse with the host cell membrane [50]. DNA sequencing studies have shown that CD4 C868T, a novel CD4 single-nucleotide polymorphism (SNP) that is highly prevalent among Africans, changes the tertiary structure of CD4, which may alter susceptibility to HIV-1 infection. The C868T (rs28919570), one of the five nonsynonymous SNPs in the CD4, results in the amino acid substitution of tryptophan for arginine in the third domain. The CD4 C868T is found to be significantly more prevalent among HIV-1-infected than among HIV-1-uninfected individuals in African populations. In Kenya, a study on commercial sex workers has shown heterozygous women for CD4 C868T to be more than twice more likely to acquire HIV-1 than those with the wild-type CD4 allele. Given the high prevalence of both HIV-1 infection and CD4 C868T in African populations, the effect of SNP on the epidemic in Africa could be dramatic [47].

However, most HIV-based co-receptor research focuses on the CCR5 co-receptor. The majority of HIV strains use the CCR5 receptor [51]. The HIV-2 strains can also use the CXCR4 receptor [45] though the CCR5 receptor is the more predominantly targeted of the two. Both the CCR5 and the CXCR4 co-receptors are seven-trans-membrane (7TM) G protein-coupled receptors [51]. Different strains of HIV work on different co-receptors, although the virus can switch to utilizing other co-receptors [51]. For example, R5X4 receptors can become the dominant HIV-1 co-receptor target in main strains. HIV-1 and HIV-2 can both use the CCR8 co-receptor [52]. The crossover of co-receptor targets for different strains and the ability of the strains to switch from their dominant co-receptor can impede the clinical treatment of HIV. Treatments such as WR321 mAb can inhibit some strains of CCR5 HIV-1, preventing cell infection [53]. The mAb causes the release of HIV-1 inhibitory β-chemokines, preventing other cells from becoming infected [54].

Little is known about genetic variations in CD4 in the context of HIV-1 mother–child transmission (MTCT), notwithstanding the relevance of the receptor in viral entry and
dissemination. However, in children exposed to HIV-1 MTCT, the carriage of the single-nucleotide polymorphism (SNP) rs28919570-T underlying the allelic variant CD4-R240W has been associated with an increased risk of transmission [55]. This variant causes OKT4 monoclonal antibody T-helper/inducer cell epitope deficiency in African–American, Caucasian and Japanese individuals [56, 57]. Similarly, a polymorphism (C868T) of the CD4 gene, which is highly prevalent among Africans, plays a significant role in determining a two-fold increase of MTCT when heterozygously expressed in Kenyan children [56]. This same mutation had no effect when expressed in the mother [58].

The C868T SNP in the CD4 receptor encodes an amino acid change that could alter its structure and influence HIV-1 infection risk. In Nairobi Kenya, a study by Choi et al. [55] followed HIV-1-infected pregnant women with their infants for 1 year postpartum. Among 131 infants, those with the 868T allele were more likely than wild-type infants to acquire HIV-1 overall with a hazard ratio (HR) of 1.92. This SNP was associated with increased susceptibility to mother-to-child HIV-1 transmission, consistent with a previous study on this polymorphism among Nairobi sex workers.

Characterization of HIV-1 genetic/antigenic variants circulating in a given population

As indicated elsewhere in this review, the HIV-1 env, CD4 and wild-CCR5 proteins are responsible for the attachment and entry of HIV into T-lymphocytes, hence influencing HIV-1 virulence and disease progression. It is also notable that a mutant allele of the β-chemokines receptor gene CCR5 bearing a 32-basepair (bp) deletion prevents cell invasion by HIV-1, and heterozygosity at this gene correlates with slowed HIV/AIDS disease progression. Equally important is the fact that antiretroviral therapy (ART) has transformed HIV infection into a treatable, chronic condition [59]. However, the emergence of mutations that cause resistance to ARVs can limit the efficacy of ARVs treatment regimens [60]. Most drug-resistant mutants of HIV-1 emerging under the selective pressure of prolonged chemotherapy are due to mutations in the HIV-1 pol gene that encodes for the reverse transcriptase (RT) enzyme [60, 61].

Sometimes recombination between strains from various regions may contribute substantially to the emergence of new HIV-1 variants including those resistant to ARVs. Generally, HIV is a highly diverse virus with significant genetic variability which may confer biological differences that could impact treatment outcomes [60, 62]. However, ARV therapy also exerts selective pressure for ARV resistance if the existing regimen is not fully suppressive. This is more likely to occur in resource-poor countries where relatively cheap and generic drugs are likely to be widely available with rare use of viral load to measure therapeutic response, and adherence to ART is likely to be poor. Even when treatment failure is evident, patients in these countries may be kept on the same regimen since the second-line regimens are more expensive [60].

The need for continued treatment for many decades calls for a long-term perspective of ART. In Kenya, HIV/AIDS was declared a national disaster in 1999 when the prevalence was at 30% among some populations in the country and is at the top of the government’s agenda since then [63]. There is a likelihood of a tremendous increase in the usage of ARVs and the development of resistance to ARVs is therefore eminent, and this will adversely affect the efficacy of the ARVs [64]. The great heterogeneity and emergence of many HIV-1 recombinants the world over [29] also mean different responses by patients to ART therapy and different immune response to the recombinants. It is important to determine
whether HIV-1 genetic/antigenic variation is random or follows a certain pattern.

Regular periodic molecular analysis of HIV-1 strains is important, especially now that subtype-specific vaccines are under consideration. Regular resistance mutation analyses are required to monitor ARV resistance and determine the association between HIV-1 strain variation(s) and high infection discordance seen among some couples in Kenya [65]. Characterization of genetic/antigenic variants circulating in a given population is essential for more effective patient management. It is also of cardinal significance to note that long-term antiretroviral therapy (ART) use in resource-limited countries leads to increasing numbers of patients with HIV/AIDS taking second-line therapy. The limited access to further therapeutic options makes essential the evaluation of second-line regimen efficacy in these resource-limited countries [66].

Results

A total of 74 articles were screened and 66 eligible articles were reviewed, four (4) of them touching on the origin and evolutionary mechanisms of the human immunodeficiency virus (HIV), while 21 articles addressed molecular characterization of the HIV-1. A total of 11 articles addressed HIV-1 treatment and ARVs resistance, whereas 13 articles addressed the influence of host genes on HIV/AIDS disease progression. Eleven (11) and 8 articles addressed the CD4 as HIV-1 receptors and characterization of HIV-1 genetic/antigenic variants circulating in a given population, respectively.

In this review, it was found that various subtypes/recombinants/inter-subtype recombinants of HIV-1 are in circulation in Kenya (Table 1 below). It was also noted that the occurrence of mutations causes resistance to ARVs and limits the efficacy of ART regimens. Heterozygous women for CD4 C868T are more than twice more likely to acquire HIV-1 than those with the wild-type CD4 allele. A mutant allele of the β-chemokines receptor gene CCR5 denoted delta ccr5 prevents cell invasion by HIV-1. Homozygotes for this mutation are resistant to infection, even after repeated high-risk exposures. Characterization of genetic/antigenic variants circulating in a given population is essential for more effective patient management since long-term antiretroviral therapy (ART) use in resource-limited countries will lead to increased numbers of patients with HIV/AIDS taking second-line therapy.

Table 1:
HIV-1 subtypes distribution in Kenya

<table>
<thead>
<tr>
<th>Region</th>
<th>Subtypes/recombinants/inter-subtype recombinants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>A1, C, and D</td>
</tr>
<tr>
<td>Northern</td>
<td>A, C, and D</td>
</tr>
<tr>
<td>Coast</td>
<td>A1, C, D, and G</td>
</tr>
</tbody>
</table>
Discussion

This review finds the distribution of HIV-1 subtypes to differ globally, regionally and nationally, in agreement with Ogbenna et al. [62] which indicates HIV-1 as a highly diverse virus with significant genetic variability which may confer biological differences that could impact treatment outcomes. In East Africa, Kenya shares the HIV-1 subtype C with Tanzania and AD recombinants with Uganda perhaps because of the cross-border mobility of these populations.

More HIV-1 subtypes and recombinants are seen circulating in Nairobi, Western and Nyanza compared to other regions (Table 1). This review indicates that true estimates of the prevalence of ARVs drug-resistant (ARVDR) HIV-1 strains among patients receiving ARV therapy (ART) are limited [30]. However, ARV resistance highly correlates with specific ARV exposure, and transmission of ARV-resistant HIV-1 strains may increase as therapy becomes more widespread.

The CD4 C868T, a novel CD4 single-nucleotide polymorphism (SNP) is highly prevalent among Africans. The C868T results in the amino acid substitution of tryptophan for arginine [47.46] a type of mutation. Since the CD4 C868T is found to be significantly more prevalent among HIV-1-infected than among HIV-1-uninfected individuals in African populations this mutation could be attributed to the heterozygous women for CD4 C868T being more than twice more likely to acquire HIV-1 than those with the wild-type CD4 allele.

This review observes the circulation of many different HIV-1 strains in Nairobi, Western and Nyanza compared to other regions in Kenya. However, there is no clear explanation for this observation. Some studies have also reported a relatively high serodiscordant rate among couples [65] and increased use of ARVs. Regular and concurrent characterization of HIV-1 genetic/antigenic variants and mutations that encode resistance in HIV-1 subtypes circulating in the whole country is necessary. Long-term antiretroviral therapy (ART) in resource-limited countries like Kenya has led to increased numbers of patients with HIV/AIDS taking second-line therapy [66], which makes the evaluation of second-line regimens efficacy essential.

Conclusion

1. Many sub-types of HIV-1 are in circulation in Kenya with uneven distribution. 2. Antiretroviral therapy (ART) has transformed HIV-1 infection into a treatable, chronic condition. 3. Drug-resistant mutants of HIV-1 have emerged due to the selective pressure of prolonged chemotherapy and recombination between strains from various regions. 4. A mutant allele of the β-chemokine receptor gene CCR5 prevents cell invasion and homozygotes for this mutation are resistant to infection. Heterozygosity at this gene correlates with slowed HIV/AIDS disease progression. 5. The CD4 C868T, a novel CD4 single-nucleotide polymorphism (SNP) is highly prevalent among Africans and in Kenya, heterozygous women for CD4 C868T are more than twice likely to acquire HIV-1 than those with the wild-type CD4 allele.

Recommendations

There is a need to: 1. Determine and map out the distribution of HIV-1 strains in Kenya and monitor their variations over time. 2. Determine the prevalence of multi-HIV-1 subtypes co-infections. 3. Determine CD4 and CCR5 genes polymorphisms among HIV-1 discordant couples in the Kenyan population. 4. Decipher groups most susceptible to HIV-1 infections in the African Kenyan population. 5. Carry out regular ARV resistance mutation analyses and their variation over time for guided HIV/AIDS chemotherapy.
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